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Use of zoledronic acid in the treatment of Paget's disease

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Abstract: This review examines the use of zoledronic acid in the treatment of Paget's disease of bone. It begins with a brief discussion of the theories of pathogenesis of Paget's disease, its clinical manifestations, and the history of bisphosphonate treatment in this disorder. Risk of oversuppression of bone by the more potent bisphosphonates and their association with avascular necrosis of the jaw are noted.

Keywords: Paget's disease of bone, bisphosphonates, zoledronic acid

The treatment of Paget's disease of bone has evolved remarkably over the last several decades, from using drugs simply to ease bone pain to using others designed to induce remission and prevent deformity. The development of potent bisphosphonates, analogs of naturally occurring pyrophosphates, has been responsible for this evolution, and in turn has driven our understanding of basic physiology of bone. This review will focus on the role of zoledronic acid (Zometa[®]; Novartis) in the treatment of Paget's disease. The potency and efficacy of zoledronic acid in Paget's disease will be considered in the context of the older bisphosphonates, the use of these drugs in other bone diseases, and the emerging data on bisphosphonates and skeletal health.

Paget's disease is thought to be a primary disorder of the osteoclast. The evidence for this is that the earliest radiographic lesion is osteolytic, and that there are abnormal numbers of osteoclasts in pagetic bone with an atypical phenotype (Mills et al 1980; Kukita et al 1990; Demulder et al 1993). The finding of intranuclear inclusions in the pagetic osteoclasts that were characteristic of paramyxoviruses (Rebel et al 1981), and the epidemiological work of Khan et al (1996) suggesting Paget's disease was more common in dog owners, led investigators to seek a viral etiology to this disease. Evidence accrued for infection of the osteoclast by measles virus or canine distemper virus in patients with Paget's disease of bone, with variable seeding of the osteoclasts in bone accounting for the distribution of the pagetic lesions in a given individual. This theory faltered as genetic probing of bone cells for evidence of transcripts of these viruses led to conflicting results (Mee 1999; Rima et al 2002; Ralston et al 2007). In 2002, Hocking et al (2002) identified a mutation in a Canadian cohort in the ubiquitin-binding sequence of the sequestosome gene, *SQSTM1*, occurring in 46% of patients with familial Paget's disease, and in 16% of patients with sporadic Paget's disease. The mutation affects a scaffolding protein p62 that is involved in osteoclast signaling, and that is presumed to enhance osteoclast activation and differentiation (Duran et al 2004). By itself, the mutation is insufficient to cause Paget's disease of bone, and environmental factors extrinsic to the osteoclast are being sought to explain the variable expression of this disease.

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Paget's disease is a focal disorder of bone metabolism, characterized by an initial phase of bone resorption that begins in subchondral bone and moves through the affected bone. The bone thickens with the deposition of woven bone admixed with lamellar bone, and the marrow is replaced by peritrabecular fibrosis associated with capillary ingrowth. The complications of Paget's disease stem from this bony overgrowth, and include deformity, bone pain, fracture, nerve compression syndromes and orthopaedic complications (Siris and Roodman 2003). In Paget's disease, the rate of osteoclast resorption of bone remains coupled to bone formation, and it is sufficient to treat the osteoclast to restore bone-remodeling rates more towards normal. Currently, all agents used to treat Paget's disease are antiresorptive in nature. Accepted therapies today include calcitonin, etidronate, tiludronate, clodronate and the newer aminobisphosphonates. This review will focus on zoledronic acid, a potent aminobisphosphonate just approved in the US for the treatment of Paget's disease of bone (April 2007). Some comments will be made about the other bisphosphonates to understand the context in which this drug was developed. The ultimate goal of treatment is to ease suffering, to prevent the complications of Paget's disease that result from the abnormal resorption and overgrowth of bone, and to restore normal bone turnover.

The bisphosphonates are analogs of inorganic pyrophosphate, a ubiquitous metabolite in all tissues. The bisphosphonates were initially shown to bind to the surface of calcium/phosphate mineral phases and impair crystal growth as well as dissolution, and were considered for various industrial applications based on their physicochemical properties. In 1968, Dr Fleisch and colleagues showed that bisphosphonates also had the biological property to inhibit osteoclastic bone resorption (Fleisch 2002). The drugs bind avidly to the calcium/phosphate inorganic mineral phase of bone, are not hydrolyzed by pyrophosphatases such as bone alkaline phosphatase, and have a sustained effect on bone resorption indices. The drugs began to be used in clinical medicine, based on these biological properties, for the treatment of Paget's disease, osteoporosis, hypercalcemia of malignancy and complications of bone metastases.

Etidronate, the first bisphosphonate approved for the treatment of Paget's disease, was noted early on to impair mineralization at doses needed to inhibit resorption. Even at low therapeutic doses (5 mg/kg), etidronate was associated with an increased risk of fracture, bone pain and incomplete biochemical response as measured by the percent reduction in serum alkaline phosphatase and urinary markers of bone resorption (Krane 1982; Evans et al 1983; Hughes et al 1995).

More potent bisphosphonates were developed that were antiresorptive at doses that would not result in bone mineralization defects (osteomalacia). The aminobisphosphonates were introduced for this reason, and as a class were remarkably well tolerated and efficacious in the treatment of Paget's disease.

The aminobisphosphonates include pamidronate, alendronate, risedronate, olpadronate, ibandronate and zoledronate. These drugs work by a mechanism distinct from etidronate. Specifically, the aminobisphosphonates inhibit farnesyl diphosphate synthase, an enzyme in the mevalonate pathway critical in the prenylation of small G-proteins that mediate cytoskeletal rearrangement in osteoclasts (Widler et al 2002). In 1994, pamidronate was approved by the FDA in the US for intravenous treatment of Paget's disease, followed by oral alendronate in 1995, and then oral risedronate. Pamidronate, at a therapeutic dose of 30–90 mg, required a prolonged infusion time of 2–6 hours. As experience with the drug grew, and higher doses were used over shorter infusion times, collapsing focal glomerulosclerosis was observed (Markowitz et al 2003), as well as clinically unsuspected osteomalacia (Adamson et al 1993). Further, in the years following a larger experience with its use, resistance to its pharmacological effects was encountered; this was described as a failure to reduce the levels of serum alkaline phosphatase by 50%–75% (Trombetti et al 1999; Rendina et al 2004). Other complications of the aminobisphosphonates were also identified such as transient flu-like symptoms with the initial infusion, hypocalcemia (Rosen and Brown 2003), and rarely iritis (Macarol and Fraunfelder 1994), or an allergic reaction.

The bisphosphonates as a class have poor oral availability. Zoledronic acid was developed as an intravenous drug that could be infused for a brief period in an ambulatory setting. Preclinical studies suggested that zoledronate was 100–850 times more potent than pamidronate *in vitro* and *in vivo* test systems, and could be administered intravenously in effective doses in 15–30 minutes (Body 1997). Preclinical trials suggested that zoledronic acid was also safer than pamidronate in terms of renal toxicity, and more effective in suppressing bone resorption for a sustained period (Green et al 1994, 1997). Using the intravenous route by-passed the issues of oral availability and gastrointestinal irritation reported with the other potent oral aminobisphosphonates alendronate and risedronate, and ensured rapid, easy delivery to bone. This regimen offered patients with Paget's disease, as well as those suffering from lytic bone metastases and osteoporosis, an opportunity to receive treatment quickly, and theoretically, less frequently.

The goal of all treatment with the aminobisphosphonates in patients with Paget's disease of bone is to provide a sustained biochemical remission in disease, and to ease suffering caused by skeletal complications of disease. These goals were being achieved in many patients with the oral bisphosphonates alendronate and risedronate (Siris et al 1996; Brown et al 1999; Reid and Siris 1999) when the first human trials with zoledronic acid in humans with Paget's disease were published in 1997 (Arden-Cordone et al 1997). Zoledronic acid was infused in 60 mL normal saline over 60 minutes. The doses of zoledronic acid tested were 24, 72, 216, and 400 μ g and responses were measured as percentage reduction from baseline of calcium/creatinine ratio and 24-hour urinary hydroxyproline excretion at 24 hours and at days 3, 7, 10, and 24. No significant changes in these bone markers were observed at the lowest doses of zoledronic acid, but at 216 μ g and 400 μ g zoledronate, a significant reduction in urinary calcium/creatinine ratio and hydroxyproline excretion were noted. No adverse effects such as fever or renal dysfunction were seen using this protocol.

In 1999, a dose- ranging study of single doses of zoledronic acid was reported (Buckler et al 1999). The primary measures of efficacy were maximum percent reduction in serum alkaline phosphatase and urinary hydroxyproline over 3 months in patients with Paget's disease. One hundred seventy-six patients were enrolled, with baseline serum alkaline phosphatases at least twice the upper limits of normal. A therapeutic response was defined as a 50% reduction in serum alkaline phosphatase from baseline or normalization following treatment. With 400 μ g, a 50% decrease from baseline serum alkaline phosphatase was seen in 46% patients, and normalization in 20%; this dose was far superior to 50 μ g, 100 μ g, 200 μ g, and placebo. Side effects such as fever, skeletal pain, and asymptomatic hypocalcemia were dose related, and transient.

Over the next few years, there were case reports of the efficacy of zoledronic acid in the treatment of Paget's disease that had proven refractory to other agents (Chung and Keen 2003); and the drug was being used at doses of 4 mg i.v. monthly in patients with cancer metastatic to bone (Derenne et al 1999; Rosen et al 2001). Zoledronic acid was also being evaluated in clinical trials in patients with osteoporosis using 4 mg once yearly (Reid et al 2002), and there was ongoing research on the anti-angiogenic properties of zoledronic acid in cancer (Fournier et al 2002; Bezzi et al 2003). During these years as well, the first reports of acute renal failure in patients receiving zoledronate were being published (Chang et al 2003; Markowitz et al 2003).

In 2005, Reid and colleagues published the pivotal double-blinded, randomized clinical trial using zoledronic acid compared to risedronate in patients with Paget's disease (Reid et al 2005). The study design combined two identical, double-blinded, randomized controlled trials, comparing zoledronic acid with risedronate. It was a 6-month trial, with patients either receiving one i.v. infusion of zoledronic acid 5 mg (177 patients) or risedronate 30 mg daily for 2 months (172 patients). Patients were well matched for age, elevation in serum alkaline phosphatase, and prior exposure to other forms of therapy. All had baseline serum alkaline phosphatase more than twice the upper limits of normal; patients with evidence of renal disease were excluded (serum CrCl <30 mL/min). Adherence to the protocol was better than 90%.

The primary end-point was normalization of the serum alkaline phosphatase level, or a reduction by 75% in 6 months. A pain scale, gait, and quality of life measures were assessed as well. At the completion of this study, a greater number of patients treated with zoledronic acid (96%) achieved this primary end-point compared to those treated with risedronate (74%, $p < 0.001$). Further, zoledronic acid provided patients with a significantly shorter median time to first therapeutic response (64 vs 89 days, $p < 0.001$). In patients with Paget's disease of bone, normalization of serum alkaline phosphatase correlates with a longer duration of biochemical remission. More patients in the zoledronic acid-treated group normalized their serum alkaline phosphatase (88.6%) than in the risedronate-treated group (57.9%), $p < 0.001$. Bone turnover markers, including serum N-terminal propeptide of Type I collagen and serum β C-telopeptide of Type I collagen measuring osteoblast function (bone formation), and urinary α C-telopeptide of Type I collagen measuring osteoclast function (bone resorption) were all suppressed into the normal range earlier and more consistently in patients treated with zoledronic acid, $p < 0.001$.

Clearly, patients had a dramatic biochemical response to treatment with zoledronic acid, with many patients having suppression of serum alkaline phosphatase into the normal range, and a sustained period of biochemical remission. At a median of 190 days following the formal trial, only 1 of 113 patients on zoledronic acid (0.9%) showed evidence of recurrent disease activity by biochemical markers, compared with 21 of 82 patients on risedronate (25.6%), $p < 0.001$. Except for transient fever and flu-like symptoms, zoledronic acid infusion was well tolerated. Eight patients in all developed hypocalcemia, severe only in one risedronate-treated patient. The mean serum creatinine "decreased slightly but

significantly by day 10" in patients receiving zoledronic acid ($p < 0.001$), but at subsequent visits the values were noted to be similar in both treatment groups. Although the study was designed to demonstrate the non-inferiority of zoledronic acid compared with risedronate in the treatment of Paget's disease, the authors concluded that "zoledronic acid appeared to be superior in terms of the degree of disease suppression, the rate of onset of effect and (on the basis of preliminary data) the persistence of these effects beyond the six-month trial period". In addition, there was a trend towards improved quality of life in patients treated with zoledronate.

In a follow-up extension trial of this preliminary study published by Hosking and colleagues in 2007, 152 patients who had been treated with zoledronic acid and 115 patients who had been treated with risedronate were followed for 18 months to determine the length of remission and durability of bone suppression (Hosking et al 2007). Patients were eligible for the extension trial if they were in biochemical remission, which was defined as normalization or 75% reduction of the serum alkaline phosphatase level. The extension period was defined as beginning after 6 months of therapy, and patients were well matched for age, prior history of bisphosphonate use, and biomarkers. A sustained therapeutic response was noted in 98% of those treated with zoledronic acid vs 57% of those treated with risedronate. In the discussion, the authors noted that "a reduction in the incidence and severity of long-term complications such as fracture and deformity may require persistent normalization of bone turnover over many years," a goal that may be achievable with zoledronic acid. In looking at determinants of relapse, it was noted that patients treated with risedronate who had experienced prior bisphosphonate therapy seemed more vulnerable to relapse than those who were treatment naïve ($p < 0.01$); this trend was not seen in those treated with zoledronate.

Is a very potent bisphosphonate such as zoledronic acid really better for patients with Paget's disease, better for an aging skeleton in general, and better in terms of safety profile? These questions are somewhat difficult to answer, since it has yet to be determined whether oversuppression of bone turnover is a significant and evolving risk. Citing the pivotal trial in the *N Engl J Med* comparing zoledronic acid with risedronate in the treatment of Paget's disease of bone, Hosking et al wrote that "(zoledronic acid) restores normal bone turnover in the majority of patients with very active Paget's disease" (Hosking et al 2007). It is a conclusion that is largely supported by sustained reductions in bone turnover markers and serum alkaline phosphatase, rather than bone

histomorphometric measurements. We have very little bone biopsy data for review. What was available showed "that the extent of the mineralizing surface was below the reference range in the zoledronic acid group ($p = 0.04$) for the comparison with the risedronate group)" (Reid et al 2005). Dr Ott, in correspondence published in the *N Engl J Med*, voiced concerns about the consequences of oversuppression of bone turnover from bisphosphonates (Ott 2004). In 2003, a case report of bisphosphonate-induced osteopetrosis was published (Whyte et al 2003), and the first cases of osteonecrosis of the jaw were described in association with the use of pamidronate and zoledronic acid in patients with bone metastases (Marx 2003). None were reported in the two studies of zoledronic acid reviewed here. Supporting the safety of zoledronic acid used in the treatment of Paget's disease of bone is a recent study looking at comparable dosing of zoledronate vs alendronate in a cohort of patients with osteoporosis. There was no oversuppression of bone formation and no impaired mineralization reported in the 23 bone biopsies obtained (McClung et al 2007).

Bisphosphonates are now approved for Paget's disease of bone, post-menopausal osteoporosis, postmenopausal osteopenia, glucocorticoid-induced osteoporosis in men and pre- and post-menopausal women, and metastatic bone disease. The consequences of the extension of indications to pre-menopausal women and the use in children with metabolic bone diseases have not been extensively studied, although recent reports suggest that these are areas of concern in terms of over suppression of bone in vulnerable populations. Odvina et al reported severe suppression of bone-turnover in fracture patients treated with long-term alendronate therapy (Odvina et al 2005). There are increasing numbers of case reports describing "osteonecrosis" of the jaw in older cancer patients, particularly those treated with monthly intravenous zoledronic acid or pamidronate (Maerevoet et al 2005; Marx et al 2005; Merigo et al 2005). All of the studies cited reflect small cohorts; but because of the prolonged retention of bisphosphonates in human bone, these observations are troubling. Against these reports are insights into the benefits of zoledronic acid in cancer treatment (Daubine et al 2007; Marten et al 2007), and in easing the pain of metastatic bone disease (Gralow and Tripathy 2007); in fracture prevention in patients with osteoporosis (Black et al 2007); and in fracture healing (Amanat et al 2007). In a recent study examining annual zoledronic acid therapy in a cohort of 3889 post-menopausal women, Black and colleagues reported important reductions in vertebral, hip, and other fractures without serious toxicity other than

atrial fibrillation. Specifically, there were no cases of osteonecrosis of the jaw (Black et al 2007). In fact, overall toxicity from zoledronic acid seems mostly predictable in the limited doses used in patients with Paget's disease of bone, and most side effects can probably be avoided by ensuring adequate amounts of vitamin D and calcium are given as supplements prior to therapy, renal function is adequate, and good dental care is obtained prior to treatment (Lipton 2007).

Theoretically, patients most susceptible to oversuppression of bone turnover include dialysis and transplant patients at risk for adynamic bone disease; children in whom normal post-translational modification of small G proteins is essential for normal growth; pre-menopausal women who may yet choose to conceive; and cancer patients undergoing dental extractions. Patients with Paget's disease of bone are less vulnerable for many reasons. They tend to be older at the time of diagnosis, treatment is limited, and exposure to prior bisphosphonate therapy may be minimal. In patients with polyostotic Paget's disease who may have multiple co-morbidities, are consuming many oral medications and require assistance in transportation to the hospital, a single dose of zoledronic acid for the treatment of Paget's disease may ease pain, improve quality of life and facilitate management. For younger persons, more likely to have monostotic disease, we think any of the newer generation aminobisphosphonates constitute adequate treatment, including alendronate and risedronate. These oral aminobisphosphonates remain good therapeutic agents in Paget's disease, and have been shown to improve radiographic outcomes, and suppress biochemical markers of active Paget's disease in many (Miller et al 1999; Reid and Siris 1999), and they may have the advantage of limiting skeletal exposure to bisphosphonates. This is unproven. In a recent study published on drug utilization of the bisphosphonates in Paget's disease of bone, inappropriate dosing regimens were quite prevalent with the oral bisphosphonates, suggesting patients may benefit from the single dose therapy offered by zoledronate treatment (Dolgitser et al 2007).

There are good data indicating that the skeletal extent of Paget's disease is diminishing as an inverse correlate with date of birth in the 20th century (Cooper et al 1999; Cundy et al 1999; Morales-Piga et al 2002; van Staa et al 2002). Even in patients with biochemical remission, abnormal bone is still evident in plain radiographs, deformities persist, hearing is not restored and bone is still abnormally vulnerable to fracture. Although the premise that early treatment of Paget's disease prevents future complications has a sound theoretical basis, there has been no published study proving this to be

true. Given the changing epidemiology of Paget's disease and the economic incentives at hand, it is unlikely that such a study will be undertaken. It seems prudent, therefore, to consider the different properties of the aminobisphosphonates, the burden of pagetic bone in the skeleton and the particular circumstances of a patient when selecting a drug for the treatment of Paget's disease.

In summary, the aminobisphosphonates, prescribed thoughtfully, are generally safe and well tolerated, and provide a means for treatment of Paget's disease, metastatic cancer of bone, osteoporosis, and other less common disorders such as osteogenesis imperfecta. In the case of Paget's disease of bone, zoledronic acid may be efficacious when other aminobisphosphonates are not, and may be particularly useful in the elderly and in those with polyostotic disease. Complications such as osteonecrosis of the jaw are exceedingly rare in patients with Paget's disease of bone treated with a bisphosphonate. It is prudent to recommend that dental procedures such as extractions or implants be carried out well before treating patients with these more potent bisphosphonates, until more is known about the predilection of the jaw for osteonecrosis and the basic pathophysiology. Finally, supplements of vitamin D and calcium should be given to all patients with Paget's disease treated with bisphosphonates.

References

- Adamson BB, Gallacher SJ, Byars J, et al. 1993. Mineralisation defects with pamidronate therapy for Paget's disease. *Lancet*, 342:1459–60.
- Amanat N, McDonald M, Godfrey C, et al. 2007. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res*, 22:867–76.
- Arden-Cordone M, Siris ES, Lyles KW, et al. 1997. Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int*, 60:415–8.
- Bezzi M, Hasmim M, Bieler G, et al. 2003. Zoledronate sensitizes endothelial cells to tumor necrosis factor-induced programmed cell death: evidence for the suppression of sustained activation of focal adhesion kinase and protein kinase B/Akt. *J Biol Chem*, 278:43603–14.
- Black DM, Delmas PD, Eastell R, et al. 2007. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*, 356:1809–22.
- Body JJ. 1997. Clinical research update: zoledronate. *Cancer*, 80:1699–701.
- Brown JP, Hosking DJ, Ste-Marie L, et al. 1999. Risedronate, a highly effective, short-term oral treatment for Paget's disease: a dose-response study. *Calcif Tissue Int*, 64:93–9.
- Buckler H, Fraser W, Hosking D, et al. 1999. Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone*, 24:81S–85S.
- Chang JT, Green L, Beitz J. 2003. Renal failure with the use of zoledronic acid. *N Engl J Med*, 349:1676–9; discussion 1676–9.
- Chung G, Keen RW. 2003. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis*, 62:275–6.
- Cooper C, Schaffheutle K, Dennison E, et al. 1999. The epidemiology of Paget's disease in Britain: is the prevalence decreasing? *J Bone Miner Res*, 14:192–7.

- Cundy T, Wattie D, Busch S, et al. 1999. Paget's disease in New Zealand: is it changing? *Bone*, 24:7S–9S.
- Daubine F, Le Gall C, Gasser J, et al. 2007. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst*, 99:322–30.
- Demulder A, Takahashi S, Singer FR, et al. 1993. Abnormalities in osteoclast precursors and marrow accessory cells in Paget's disease. *Endocrinology*, 133:1978–82.
- Derenne S, Amiot M, Barille S, et al. 1999. Zoledronate is a potent inhibitor of myeloma cell growth and secretion of IL-6 and MMP-1 by the tumoral environment. *J Bone Miner Res*, 14:2048–56.
- Dolgitser M, Stern L, Katz LM, et al. 2007. *Manag Care Interface*, 20:33–40.
- Duran A, Serrano M, Leitges M, et al. 2004. The atypical PKC-interacting protein p62 is an important mediator of RANK-activated osteoclastogenesis. *Dev Cell*, 6:303–9.
- Evans RA, Dunstan CR, Hills E, et al. 1983. Pathologic fracture due to severe osteomalacia following low-dose diphosphonate treatment of Paget's disease of bone. *Aust N Z J Med*, 13:277–9.
- Fleisch H. 2002. Development of bisphosphonates. *Breast Cancer Res*, 4:30–4.
- Fournier P, Boissier S, Filleul S, et al. 2002. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res*, 62:6538–44.
- Gralow J, Tripathy D. 2007. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage*, 33:462–72.
- Green JR, Muller K, Jaeggi KA. 1994. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res*, 9:745–51.
- Green JR, Seltene Y, Jaeggi KA, et al. 1997. Renal tolerability profile of novel, potent bisphosphonates in two short-term rat models. *Pharmacol Toxicol*, 80:225–30.
- Hocking LJ, Lucas GJ, Daroszewska A, et al. 2002. Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. *Hum Mol Genet*, 11:2735–9.
- Hosking D, Lyles K, Brown JP, et al. 2007. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. *J Bone Miner Res*, 22:142–8.
- Hughes DE, Wright KR, Uy HL, et al. 1995. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. *J Bone Miner Res*, 10:1478–87.
- Khan SA, Brennan P, Newman J, et al. 1996. Paget's disease of bone and unvaccinated dogs. *Bone*, 19:47–50.
- Krane SM. 1982. Etidronate disodium in the treatment of Paget's disease of bone. *Ann Intern Med*, 96:619–25.
- Kukita A, Chenu C, McManus LM, et al. 1990. Atypical multinucleated cells form in long-term marrow cultures from patients with Paget's disease. *J Clin Invest*, 85:1280–6.
- Lipton A. 2007. The safety of zoledronic acid. *Expert Opin Drug Saf*, 6:305–13.
- Macarol V, Fraunfelder FT. 1994. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol*, 118:220–4.
- Maerevoet M, Martin C, Duck L. 2005. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med*, 353:99–102; discussion 99–102.
- Markowitz GS, Fine, PL, Stack, JJ, et al. 2003. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int*, 64:281–9.
- Marten A, Lilienfeld-Toal M, Buchler MW, et al. 2007. Zoledronic acid has direct antiproliferative and antimetastatic effect on pancreatic carcinoma cells and acts as an antigen for delta2 gamma/delta T cells. *J Immunother*, 30:370–7.
- Marx RE. 2003. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*, 61:1115–7.
- Marx RE, Sawatari Y, Fortin M, et al. 2005. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg*, 63:1567–75.
- McClung M, Recker R, Miller P, et al. 2007. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*, 41:122–8.
- Mee AP. 1999. Paramyxoviruses and Paget's disease: the affirmative view. *Bone*, 24:19S–21S.
- Merigo E, Manfredi M, Meleti M, et al. 2005. Jaw bone necrosis without previous dental extractions associated with the use of bisphosphonates (pamidronate and zoledronate): a four-case report. *J Oral Pathol Med*, 34:613–7.
- Miller PD, Brown JP, Siris ES, et al. 1999. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Paget's Risedronate/Etidronate Study Group. *Am J Med*, 106:513–20.
- Mills BG, Singer FR, Weiner LP, et al. 1980. Cell cultures from bone affected by Paget's disease. *Arthritis Rheum*, 23:1115–20.
- Morales-Piga AA, Bachiller-Corral FJ, Abaira V, et al. 2002. Is clinical expressiveness of Paget's disease of bone decreasing? *Bone*, 30:399–403.
- Odvina CV, Zerwekh JE, Rao DS, et al. 2005. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab*, 90:1294–301.
- Ott SM. 2004. Ten years of alendronate treatment for osteoporosis in postmenopausal women. *N Engl J Med*, 351:190–2; author reply 190–2.
- Ralston SH, Afzal MA, Helfrich MH, et al. 2007. Multicenter blinded analysis of RT-PCR detection methods for paramyxoviruses in relation to Paget's disease of bone. *J Bone Miner Res*, 22:569–77.
- Rebel A, Basle M, Pouplard A, et al. 1981. Towards a viral etiology for Paget's disease of bone. *Metab Bone Dis Relat Res*, 3: 235–8.
- Reid IR, Brown JP, Burckhardt P, et al. 2002. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med*, 346:653–61.
- Reid IR, Miller P, Lyles K, et al. 2005. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med*, 353:898–908.
- Reid IR, Siris E. 1999. Alendronate in the treatment of Paget's disease of bone. *Int J Clin Pract Suppl*, 101:62–6.
- Rendina D, Mossetti G, Viceconti R, et al. 2004. Risedronate and pamidronate treatment in the clinical management of patients with severe Paget's disease of bone and acquired resistance to bisphosphonates. *Calcif Tissue Int*, 75:189–96.
- Rima BK, Gassen U, Helfrich MH, et al. 2002. The pro and con of measles virus in Paget's disease: con. *J Bone Miner Res*, 17:2; author reply 2293.
- Rosen LS, Gordon D, Kaminski M. 2001. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J*, 7:377–87.
- Rosen CJ, Brown S. 2003. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. *N Engl J Med*, 348:1503–4.
- Siris E, Roodman GD. 2003. In *Primer on the Metabolic Bone Diseases* Favus MJ ed. Washington, DC: ASBMR, pp. 495–506.
- Siris E, Weinstein RS, Altman R, et al. 1996. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab*, 81:961–7.
- Trombetti A, Arlot M, Thevenon J, et al. 1999. Effect of multiple intravenous pamidronate courses in Paget's disease of bone. *Rev Rhum Engl Ed*, 66:467–76.
- van Staa TP, Selby P, Leufkens HG, et al. 2002. Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res*, 17:465–71.
- Whyte MP, Wenkert D, Clements KL, et al. 2003. Bisphosphonate-induced osteopetrosis. *N Engl J Med*, 349:457–63.
- Widler L, Jaeggi KA, Glatt M, et al. 2002. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J Med Chem*, 45:3721–38.